REMARKS

The Action indicated that claims 6-9, 12 and 13 were pending at the issuance of the instant Office Action. The rejections set forth in the Office Action are traversed by argument below.

1. Drawings

The Action objected to the proposed amendments of the descriptions of Figures 2 and 3 for allegedly adding new matter to the specification. Applicants have deleted Figures 2 and 3 and have amended the specification to remove references to Figures 2 and 3, thereby rendering the objections moot.

2. Rejection of claims under 35 U.S.C. § 112, first paragraph

Claims 6-9 and 12-13 stand rejected as allegedly not satisfying the written description requirement of 35 U.S.C. §112, first paragraph. The Action specifically asserts that there is no proper antecedent basis for the limitation of an amino acid sequence from a non-VGF protein covalently linked to an amino acid sequence as set forth in SEQ ID NO: 7. The Action further asserts that Applicants have introduced a negative limitation to exclude the VGF polypeptide described by Salton et al. (1991). Applicants respectfully traverse.

Applicants submit that the phrase "non-VGF protein" is not a negative limitation intended to exclude the larger VGF polypeptide described by Salton et al., because by definition a VGF fusion protein excludes the Salton VGF polypeptide. One of skill in the art recognizes that a fusion polypeptide comprises two different proteins or portions of two different proteins fused together, either directly or via a linker or adapter sequence. Applicants have attached herewith a copy of page 250 from the Oxford Dictionary of Biochemistry and Molecular Biology, which states that the term "fusion" is "(in molecular biology) the act, process, or result of artificially linking genes that code for two different proteins, with the aim of generating a **fusion protein**" (OXFORD DICTIONARY OF BIOCHEMISTRY AND MOLECULAR BIOLOGY, Revised Edition 2000, A.D. Smith, Ed., Oxford University Press, Oxford). In addition, the Glossary of Biotechnology and Genetic Engineering (Food and Agriculture Organization of the United Nations, 1999, http://www.fao.org/DOCREP/003/X3910E/X3910E00.htm#TopOfPage)

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defines a **fusion protein** as "a polypeptide made from a recombinant gene that contains portions of two or more different genes."

One of skill in the art recognizes that Salton et al. teach a VGF polypeptide, not a VGF *fusion* polypeptide. Indeed, Salton et al. teach a rat VGF protein, which is an ortholog of the human VGF polypeptide. A fusion polypeptide, by definition, is not an ortholog. The specification defines fusion polypeptide in a manner that is consistent with this ordinary and usual understanding at page 9, lines 11-13 as follows:

> The term "VGF fusion polypeptide" refers to a fusion of one or more amino acids (such as a heterologous peptide or polypeptide) at the amino or carboxyl-terminus of a VGF polypeptide, fragment, ortholog, variant, or derivative.

One of skill in the art recognizes that the phrase "such as a heterologous peptide" as used in this context does not encompass an amino acid sequence from a VGF protein, but rather a sequence from some other protein (*i.e.* a non-VGF protein), because a VGF *fusion* polypeptide, by definition, cannot be a VGF polypeptide.

The Action asserts that the specification fails to "state that 'heterologous' amino acid residues must be derived from only 'a non-VGF protein'." Applicants respectfully submit that such an explicit statement is not required in view of the understanding of the term in the art as it is related to "fusion polypeptide" in the specification. In addition, the specification provides non-limiting examples of heterologous peptides and polypeptides at page 19, line 28 to page 20, line 7. In keeping with the art recognized definition of a fusion protein, these non-limiting examples are non-VGF proteins. These specific heterologous polypeptides and peptides are provided as representative examples of non-VGF proteins that can be fused to the VGF polypeptide of SEQ ID NO: 7. These explicit examples recited in the specification when combined with the meaning of VGF fusion polypeptide as understood by those of skill in the art imply that "heterologous" amino acid residues must be derived from only "a non-VGF protein." Thus, while Applicants do not believe that the specification is deficient for lacking an explicit statement that the heterologous amino acid sequence in a VGF fusion polypeptide must be derived from a non-VGF protein, Applicants note that the specification implicitly teaches that a

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heterologous peptide or polypeptide is a non-VGF protein.

Applicants' representative discussed the instant Office Action with Examiner Hayes on April 6, 2004. Consistent with the Examiner's helpful suggestions, Applicants have introduced new claims 22 and 23. New claim 22 recites that the VGF fusion polypeptides of the invention are fused to amino acid sequences of non-VGF proteins that: aid in detection of the fusion polypeptide; aid in isolation of the fusion polypeptide; promote oligomerization of the fusion polypeptide; or increase stability of the fusion polypeptide. The specification at page 19, line 28 to page 20, line 6 specifically describes such fusion polypeptides. For example, an epitope can aid in detection and/or isolation of fusion polypeptides, a leucine zipper domain can promote oligomerization of fusion polypeptides, and that an immunoglobulin constant region or a fragment thereof can increase stability of fusion polypeptides. One of skill in the art will readily recognize and identify additional sequences that provide such functions.

New claim 23 recites that the VGF fusion polypeptides of the invention are fused to an amino acid sequence of a non-VGF protein that: is a transmembrane receptor protein or a portion thereof; is a ligand or a portion thereof that binds to a transmembrane receptor protein; is an enzyme or portion thereof that is catalytically active; or has a therapeutic activity different from the VGF polypeptide that has an amino acid sequence as set forth in SEQ ID NO: 7. Recitation of these heterologous polypeptides or peptides is found at page 19, line 28 to page 21, line 7. Transmembrane receptor proteins and their ligands are widely known in the art, as are catalytically active enzymes. In addition, the specification describes several examples of therapeutic proteins, including N-terminus of CD30-L, IL-10, TNF receptor, TNF receptor, CD4 receptor, N-terminus of IL-2, C-terminus of OPG, N-terminus of leptin, and CTLA-4 (see Table III on page 21).

The specification provides instructions for generating fusion polypeptides of the invention on page 20, and one of skill in the art can generate a fusion protein using well known techniques, such as those described in Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (Cold Spring Harbor Laboratories, 1989). Consequently, Applicants submit that the claims satisfy the requirements of 35 USC § 112, first paragraph. Applicants respectfully

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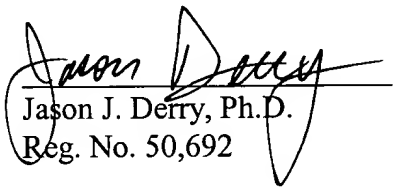
contend that all conditions of patentability are met in the pending claims. Allowance of the claims is thereby respectfully solicited.

If Examiner Hayes believes it to be helpful, he is invited to contact the undersigned representative by telephone at (312) 913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

Date: August 19, 2004

By: 
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Fusidium coccineum. Fusidic acid is active particularly against Gram-positive organisms, especially *Staphylococcus* spp. It prevents translocation during protein synthesis and inhibits the accumulation of ppGpp.

fusiform spindle-shaped; elongated and tapering at both ends.

fusion 1 the act or process of melting. 2 the act or process of melting together or uniting. 3 the process whereby two membranes are joined together, as in **cell fusion**. 4 the process whereby nuclei of light elements are united to form nuclei of heavier elements with the release of energy: **nuclear fusion**. 5 the state of being fused. 6 something produced by fusion. 7 *(in molecular biology)* the act, process, or result of artificially linking genes that code for two different proteins, with the aim of generating a **fusion protein**.

fusion protein an expression product resulting from the fusion of two genes. Such a protein may be produced, e.g., in recombinant DNA expression studies or, naturally, in certain viral **oncogenes** in which the oncogene is fused to ***gag***. Their production sometimes results from the need to place a cloned eukaryotic gene under the control of a bacterial promoter for expression in a bacterial system; sequences of the bacterial system are then frequently expressed linked to the eukaryotic protein. Fusion proteins are used for the analysis of structure, purification, function, and expression of heterologous gene products.

fusogen any agent, or set of conditions, that gives rise to fusion of membranes, including cell membranes (and hence of cells). Killed Sendai virus was formerly much used for this purpose but now polyethylene glycol is commonly used as a fusogen particularly in the preparation of hybridomas for the production of monoclonal antibodies. —**fusogenic** *adj.*

futile cycle any metabolic cycle that, if not controlled, acts as an ATPase and hence converts chemical energy (stored as ATP) to heat. For example, a coupling of phosphofructokinase, which converts fructose 6-phosphate to fructose 1,6-bisphosphate at the expense of ATP, with fructose-bisphosphatase, which hydrolyses fructose 1,6-bisphosphate to fructose 6-phosphate and (inorganic) phosphate, can form a cyclic process whose net effect is merely the hydrolysis of ATP to ADP and phosphate. A futile cycle may be an important control mechanism in some physiological conditions.

fuzzy coat *or* **fuzzy layer** the indistinct layer seen on electron microscopy outside the cell coat of various eukaryotic cells, e.g. cells of mammalian intestinal epithelium and a number of single-celled amoebae. It is composed principally of glycoproteins.

Fv fragment the N-terminal part of the **Fab fragment** of an immunoglobulin molecule, consisting of the variable portions of one light chain and one heavy chain.

FYN a gene family encoding nonreceptor tyrosine kinases of the Src family (*see* ***src***) that are implicated in the control of cell growth. The gene product, $p59^{fyn}$, associates with the p85 subunit of **1-phosphatidylinositol 3-kinase**. The proteins undergo myristoylation and phosphorylation on serine and tyrosine residues; overexpression transforms fibroblasts. Example, database code KFYN_HUMAN, 536 amino acids (60.56 kDa). The alternative gene symbols are *SYN* (from *src/yes*-related novel gene) and *SLK*..